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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,134	10/20/2002	Chandrasekhar Satishchandran	AM100013	5538

25291 7590 08/07/2006

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 08/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,134	SATISHCHANDRAN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68-173* is/are pending in the application.

4a) Of the above claim(s) *68-106,168 and 169* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *107-168 and 171-173* is/are rejected.

7)☒ Claim(s) *118, 121-122,141, 171* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 05/22/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 11/22/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 68-173 are pending. Claims 107-168 and 171-173 are currently under examination. Claims 68-106 and 169-170 are withdrawn as being drawn to a non-elected invention.

Election/Restrictions

Applicant's election with traverse of the Restriction requirement in the reply filed on 10/20/2005 is acknowledged. The traversal is on the ground(s) that a search of RNA interference would encompass any references useful in the examination of methods and nucleic acid compositions useful in RNA interference. This is not found persuasive because a search for an isolated nucleic acid molecule would not necessarily reveal art on a method of inducing RNAi of a target gene and further would not necessarily reveal art on a multitarget partially double stranded RNA molecule and further would not

necessarily reveal art on a method of making a composition comprising two or more different double stranded RNA molecule. As stated in the previous Office action filed on 09/20/2005, the subject matter is divergent and non-coextensive and it is therefore a burden to search these inventions in a single application.

The requirement is still deemed proper and is therefore made FINAL.

Priority

Claims 107-136, 139, 141-143 and 146-147 of the instant application are accorded the priority date of 10/20/2002, the filing date of the instant application. Claims 137-140, 144-145 and 148-173 are accorded a priority date of 04/19/2000. The instant application does not receive the benefit of the earlier filing priority applications because the instantly cited multitarget partially double stranded RNA molecule, is not supported by the specifications or claims of the priority applications and thus not supported by 35 U.S.C. § 112 first paragraph.

Claims 107-136, 141-143 and 146-147 are drawn to a multitarget partially double stranded RNA comprising two or more different double stranded RNA sequences that are substantially homologous and complementary to two or more sequences of a target gene. Claims 137-140, 144-145 and 148-173 are drawn to an expression vector wherein said vector encodes two or more different double stranded RNA sequences that are homologous and complementary to two or more sequences of at least one target gene.

Claims 107-136, 141-143 and 146-147 are accorded a priority date of 10/20/2002 because the prior filed applications do not provide adequate support. The prior-filed applications PCT/US00/10555 and 60/130,377 disclose a partially double stranded polynucleotide 100-1000 nucleotides in length, preferably 200 nucleotides in length wherein a minimum of 11-30 nucleotides of the polynucleotide is double-stranded to increase stability and wherein said entire RNA sequence may be double stranded. Further, the prior filed applications disclose a method of producing a partially double stranded RNA in DNA expression vectors.

The prior-filed applications do not disclose or contemplate a multitarget partially double stranded RNA molecule comprising two or more different double stranded RNA sequences wherein the two different double stranded RNA sequences are substantially homologous and complementary to a least one target gene or more than one target gene. Applicant points to page 8, lines 19-20 as support for a multitarget partially double stranded RNA molecule and points to page 9, lines 7-8 as support for a multitarget partially double stranded RNA molecule comprising two or more different double stranded RNA sequences wherein the two different double stranded RNA sequences are substantially homologous and complementary to a least one target gene or more than one target gene.

The specification as filed does provide support for a multitarget partially double stranded RNA molecule and does provide support for the two double stranded portions at both termini. However the specification on page 9, lines 5-8 disclose the function of the double stranded region is "to keep the RNA molecule stable". Nowhere in the

specification is it disclosed that the partially double stranded RNA molecule comprises two different double stranded RNA sequences wherein the two different double stranded RNA sequences are substantially homologous and complementary to a least one target gene or more than one target gene.

Further, the specification discloses, on page 9 lines 10-20, that the entire sequence of the RNA can be double stranded (i.e. one double stranded RNA molecule) and this double stranded RNA sequence is substantially homologous to the target gene. Applicants point to page 37, lines 1-6 as support for the double stranded sequences of the RNA molecule having homology to the target gene. The example at page 37, lines 1-6 disclose a 600 bp dsRNA targeted to gag gene of HIV. The specification and the example on page 37 do not provide support for a multitarget partially double stranded RNA sequence comprising *two or more* different double stranded RNA sequences substantially homologous and complementary to at least one or more target genes.

Claim 139 is drawn to an expression vector wherein said vector encode two or more different double stranded sequences wherein each different double stranded RNA sequences comprise at least 11 to 30 nucleotides involved in the double stranded sequence. The specification on page 17, lines 16-17 disclose the RNA molecule can be complete or partially double stranded and on page 20, lines 7-16, the specification discloses expression vectors designed to produce said RNA as described. Additionally the specification discloses the entire sequence of the RNA molecule can be double stranded, however the specification discloses the RNA polynucleotide sequence is 100 to 10,000 polynucleotides in length and more desirable at least 200 nucleotides.

Therefore, while the entire RNA sequence can be double stranded, this RNA polynucleotide is disclosed to be at a minimum 100 nucleotides in length. The specification does not contemplate an expression vector wherein said vector encodes two or more different double stranded sequences wherein each different double stranded RNA sequences comprise at least 11 to 30 nucleotides involved in the double stranded sequence.

Claims 137-140, 144-145 and 148-173 are accorded a priority date of 04/19/2000 because the prior filed application 60/137,377 does not provide adequate support. The prior-filed applications PCT/US00/10555 and 60/130,377 disclose a partially double stranded polynucleotide 100-1000 nucleotides in length, preferably 200 nucleotides in length wherein a minimum of 11-30 nucleotides of the polynucleotide is double-stranded to increase stability and wherein said entire RNA sequence may be double stranded. Further, the prior filed applications disclose a method of producing a partially double stranded RNA in DNA expression vectors. However, the prior filed application 60/130,377 does not provide support for an expression vector wherein said vector encodes two or more different double stranded RNA sequences.

If Applicant believes the prior applications provide support then applicant must point, with particularity, to where such support can be found in the specification of the prior applications.

New Claim Objections and Rejections

Claim Objections

Claims 141 and 171 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 141 and 171 are drawn to an expression vector of claim 137 wherein said vector encodes a multitarget partially double stranded RNA molecule encoding two or more different double stranded RNA. Claim 137 is drawn to an expression vector encoding two or more different double stranded RNA sequences complementary to one or more sequences (i.e. a multitarget double stranded RNA) and therefore claims 141 and 171 fail to further limit claim 137.

Claim 118 and dependent claims 121-122 are objected to as being dependent on a non-elected claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 107-136, 139, 141-143 and 146-147 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The

claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, MPEP §2163 states, in part "...a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." Moreover, the written description requirement for a genus may be satisfied through sufficient description of a representative number of species by "...disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between functional and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

Claims 107-136, 141-143 and 146-147 are drawn to a multitarget partially double stranded RNA comprising two or more different double stranded RNA sequences that are substantially homologous and complementary to two or more sequences of a target gene. Claim 139 is drawn to an expression vector wherein said vector encodes two or more different double stranded sequences wherein each different double stranded RNA sequences comprise at least 11 to 30 nucleotides involved in the double stranded sequence.

The specification does not provide adequate support for a multitarget partially double stranded RNA molecule comprising two or more different double stranded RNA

sequences wherein the two different double stranded RNA sequences are substantially homologous and complementary to a least one target gene or more than one target gene. The specification as filed does provide adequate support for a multitarget partially double stranded RNA molecule and does provide adequate support for the two double stranded portions at both termini. Further, the specification does not contemplate an expression vector wherein said vector encodes two or more different double stranded sequences wherein each different double stranded RNA sequences comprise at least 11 to 30 nucleotides involved in the double stranded sequence.

The specification on page 9 lines 5-8 discloses the function of the double stranded region is "to keep the RNA molecule stable". Nowhere in the specification is it disclosed that the partially double stranded RNA molecule comprises two different double stranded RNA sequences wherein the two different double stranded RNA sequences are substantially homologous and complementary to a least one target gene or more than one target gene.

Applicant argues, "[a] partially double stranded molecule containing at least one segment having homology to a target sequence implicitly contains one or more different double stranded regions." One of skill in the art would not reasonably conclude that because a partially double stranded molecule is described as having at least one segment having homology to a target sequence, it would therefore have one or more different double stranded regions. Furthermore, one of skill in the art would not reasonably conclude that the double stranded region of the partially double stranded RNA molecule would be homologous to the target sequence because the specification

discloses the double stranded region is intended to keep the molecule stable. Additionally, while the example on page 37 disclose a 600 bp double stranded RNA molecule that targets the gag gene of HIV, one of skill in the art would not reasonably conclude that this dsRNA has more than one double stranded region wherein the regions are homologous to the target gene. Moreover, one of skill in the art would not reasonably conclude that the disclosed expression vector encodes different double stranded RNA wherein the double stranded RNA comprises at least 11 to 30 nucleotides because the specification discloses the RNA polynucleotide sequence is 100 to 10,000 polynucleotides in length and more desirable at least 200 nucleotides.

Therefore, in the instant application, Applicants have not shown possession of a multitarget partially double stranded RNA comprising two or more different double stranded RNA sequences that are substantially homologous and complementary to two or more sequences of a target gene nor have Applicants shown possession an expression vector wherein said vector encode two or more different double stranded sequences wherein each different double stranded RNA sequences comprise at least 11 to 30 nucleotides involved in the double stranded sequence.

Applicants are reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 170-173 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 107-173 are drawn to a multitarget partially double stranded RNA comprising two or more different double stranded RNA sequences that are *substantially homologous and complementary to two or more sequences* of a target gene or an expression vector encoding a multitarget partially double stranded RNA comprising two or more different double stranded RNA sequences that are *substantially homologous and complementary to two or more sequences* of a target gene. It is unclear how the partially double stranded RNA sequences can be both substantially homologous and complementary to the target sequence. It is understood that the double stranded region can comprise sequences wherein one strand is homologous to a target gene and the other strand is complementary to the target gene, but is unclear how the non-double stranded region of the partially double stranded RNA sequence can be both homologous and complementary to the target sequence.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 107-110, 113-116, 123-141, 144-149, 156, 163-168 and 171-173 are rejected under 35 U.S.C. 102(a) as being anticipated by Leirdal et al. (Biochem and Biophysic Res. Comm. 2002).

The instant claims are drawn to a multitarget partially double-stranded RNA molecule comprising two or more different double stranded RNA sequences that are substantially homologous and complementary to two or more sequences of at least one target gene or substantially homologous and complementary to two or more sequences of more than one target gene, wherein at least 11 to 30 nucleotides are involved in the double stranded RNA molecule, wherein said double stranded region comprises at least 50% homology to a target gene, wherein said double stranded region comprises a sense and antisense separated by a non-base paired polynucleotide region and is separated by cleavage sequences, wherein the target gene is associated with a disease in a mammal such as a cancer associated gene, wherein the target gene is selected from a transcribed, non-transcribed, coding, non-coding, exon-containing, regulatory or promoter sequence, wherein the double stranded region lacks a polyadenylation signal, wherein a composition comprises said RNA, wherein a DNA molecule encodes said

RNA, wherein an expression vector encodes said RNA, wherein said RNA is expressed using a promoter and wherein said vector is plasmid, phage or recombinant vector. The instant claims are further drawn to an expression vector encoding two or more different double stranded RNA sequences that are substantially homologous and complementary to two or more sequences of at least one target gene, wherein at least 11 to 30 nucleotides are involved in the double stranded RNA molecule, wherein said double stranded region comprises at least 50% homology to a target gene, wherein said double stranded region comprises a sense and antisense separated by a non-base paired polynucleotide region, is a hairpin RNA and is separated by cleavage sequences, wherein said RNA sequences are expressed using a promoter, wherein said vector is plasmid, phage or recombinant vector, wherein the target gene is associated with a disease in a mammal such as a cancer associated gene, wherein the target gene is selected from a transcribed, non-transcribed, coding, non-coding, exon-containing, regulatory or promoter sequence, wherein the double stranded region lacks a polyadenylation signal and wherein a composition comprises said RNA.

Leirdal et al. teach a multitarget partially double stranded RNA molecule comprising two different double stranded RNA sequences that are complementary to a GFPsi1 sequence and a PKCαsi3 sequence which is responsible for apoptosis in glioma cells (see Figure 1 and page 747). Leirdal et al. teach the double stranded regions comprises sequences of 30 contiguous sequences that have at least 50% homology to the target gene and are complementary to the target gene and teach each double stranded region comprises an antisense and sense strand separated by a non-

base paired hairpin loop (see Figure 1). Leirdal et al. teach the partially double stranded RNA molecule comprises a single stranded region that is a cleavage site for endoribonuclease (see column 1, page 746). Leirdal et al. teach the partially double stranded sequence is transcribed in vitro by a DNA template comprising a T7 promoter and teach a pEGFP-N3 expression vector for expression of GFP and additionally teach the use of expression vectors comprising pol III promoters such as U6 for efficient expression of double stranded RNA (see column 1, page 744 and page 747). Leirdal et al. teach a composition comprising a partially double stranded RNA and a liposome to facilitate uptake into transfected cells (see page 745).

Thus, Leirdal et al. anticipates claims of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 107-148, 156-168 and 171-173 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taira et al. (cited on PTO Form 892 filed 11/22/2005) and Fire et al. (US Patent No. 6,506,559).

The instant claims are drawn to a multitarget partially double-stranded RNA molecule comprising two or more different double stranded RNA sequences that are

substantially homologous and complementary to two or more sequences of at least one target gene or substantially homologous and complementary to two or more sequences of more than one target gene, wherein at least 11 to 30 nucleotides are involved in the double stranded RNA molecule, wherein said double stranded region comprises at least 50% homology to a target gene, wherein said partially double stranded RNA molecule is between 100 to 10,000 polynucleotides in length, wherein said double stranded region comprises a sense and antisense separated by a non-base paired polynucleotide region and is separated by cleavage sequences, wherein the target gene is from a pathogen such as a virus, wherein the target gene is associated with a disease in a mammal such as a cancer associated gene, wherein the target gene is selected from a transcribed, non-transcribed, coding, non-coding, exon-containing, regulatory or promoter sequence, wherein the double stranded region lacks a polyadenylation signal, wherein a composition comprises said RNA, wherein a DNA molecule encodes said RNA, wherein an expression vector encodes said RNA, wherein said RNA is expressed using a promoter and wherein said vector is plasmid, phage or recombinant vector. The instant claims are further drawn to an expression vector encoding two or more different double stranded RNA sequences that are substantially homologous and complementary to two or more sequences of at least one target gene, wherein at least 11 to 30 nucleotides are involved in the double stranded RNA molecule, wherein said double stranded region comprises at least 50% homology to a target gene, wherein said double stranded region comprises a sense and antisense separated by a non-base paired polynucleotide region, is a hairpin RNA and is separated by cleavage sequences, wherein said RNA

sequences are expressed using a promoter, wherein said vector is plasmid, phage or recombinant vector, wherein the target gene is from a pathogen such as a virus, wherein the target gene is associated with a disease in a mammal such as a cancer associated gene, wherein the target gene is selected from a transcribed, non-transcribed, coding, non-coding, exon-containing, regulatory or promoter sequence, wherein the double stranded region lacks a polyadenylation signal and wherein a composition comprises said RNA.

Taira et al. teach multitarget partially double stranded RNA ribozyme molecules comprising from two or more different double stranded RNA sequences that are substantially homologous and complementary to 2 or more sequences of a HIV target gene (see Figure 3). Taira et al. further teach said multitarget partially double stranded RNA molecule comprises a sense polynucleotide and an antisense polynucleotide separated by a non-base paired sequence and the sense and antisense polynucleotide form a hairpin (see Figure 9), two or more different double stranded RNA sequences are separated by cleavage sequences, the cleavage sequences are autocatalytic cleavage sites and the multitarget partially double stranded RNA lacks a polyadenylation signal (see Figures 7A). Taira et al. further teach the multitarget partially double stranded RNA molecule can target one gene or more than one gene (see column 7, lines 23-29) and the multitarget ribozyme can be expressed from one single RNA molecule or from different RNA strands (see column 2, lines 29-59). Taira et al. teach a DNA molecule encoding the multitarget partially double stranded RNA molecule or two or more double stranded RNA molecules and further teach a plasmid

expression vector wherein the partially double stranded RNA molecule is expressed using a T7 bacteriophage promoter (see Figure 3). Taira et al. further teach an expression vector for reducing or inhibiting the function of the target gene wherein the expression vector encodes two or more double stranded RNA sequences complementary to two or more target sequences in one target gene (see Figure 13). Taira et al. does not specifically teach the double stranded regions of said ribozyme are homologous and complementary to the target gene.

Fire et al. teach double stranded RNA wherein the duplex regions of the RNA are capable of hybridizing with the target gene wherein the length of the duplex regions are from 25 to 400 bases (see columns 7-8). Fire et al. teach expression vectors comprising T7 polymerase promoters and teach the target gene may be derived from any cell of any organism wherein the organism may be a plant, animal or human (see column 8, lines 12-20). Fire et al. additionally teach the target gene may derived from any pathogen or any cell already infected by a pathogen such as HIV for example (see column 10, lines 8-18). Fire et al. teach the use of double stranded RNA for RNA inference is an effective alternative to antisense methodologies.

It would have been obvious to one of skill in the art to make a multitarget double stranded RNA wherein said double stranded RNA targets at least one or more than one target gene.

One would have been motivated to make a multitarget double stranded RNA targeted to two or more sequences of at least one target gene because Taira et al. teach because of the mutability of viral target genes, such as HIV, designing effective

therapeutic inhibitors of expression of said target gene is hindered and one way to overcome this mutability rate of HIV is to target multiple sites simultaneously (see column 2, lines 29-59). One would have been motivated to use double stranded RNA because Fire et al. teach double stranded RNA capable of initiating RNA interference is more sequence specific alternative to reducing expression of a target gene than antisense type mechanisms as taught by Taira et al. (see columns 1-3).

One would have had a reasonable expectation of success given that Taira et al. teach construction of multitarget ribozyme directed to several different sequences of an HIV target gene and Fire et al. teach gene inhibition using double stranded RNA wherein said duplex region is complementary to said target gene.

Thus, in absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Claims 107-168 and 171-173 are rejected under 35 U.S.C. 103(a) as being unpatentable over Werther et al. (U.S. Patent No. 5,929,040), Fire et al. (US Patent No. 6,506,559), Heifetz et al (WO 99/61631) and Thompson et al. (U.S. Patent No. 6,146,886).

The instant claims are drawn to a multitarget partially double-stranded RNA molecule comprising two or more different double stranded RNA sequences that are substantially homologous and complementary to two or more sequences of at least one

target gene or substantially homologous and complementary to two or more sequences of more than one target gene, wherein at least 11 to 30 nucleotides are involved in the double stranded RNA molecule, wherein said double stranded region comprises at least 50% homology to a target gene, wherein said partially double stranded RNA molecule is between 100 to 10,000 polynucleotides in length, wherein said double stranded region comprises a sense and antisense separated by a non-base paired polynucleotide region and is separated by cleavage sequences, wherein the target gene is from a pathogen such as a virus, wherein the target gene is associated with a disease in a mammal such as a cancer associated gene, wherein the target gene is selected from a transcribed, non-transcribed, coding, non-coding, exon-containing, regulatory or promoter sequence, wherein the double stranded region lacks a polyadenylation signal, wherein a composition comprises said RNA, wherein a DNA molecule encodes said RNA, wherein an expression vector encodes said RNA, wherein said RNA is expressed using a promoter and wherein said vector is plasmid, phage or recombinant vector. The instant claims are further drawn to an expression vector encoding two or more different double stranded RNA sequences that are substantially homologous and complementary to two or more sequences of at least one target gene, wherein at least 11 to 30 nucleotides are involved in the double stranded RNA molecule, wherein said double stranded region comprises at least 50% homology to a target gene, wherein said double stranded region comprises a sense and antisense separated by a non-base paired polynucleotide region, is a hairpin RNA and is separated by cleavage sequences, wherein said RNA sequences are expressed using a promoter or two or more different promoters, wherein

said vector is plasmid, phage or recombinant vector, wherein the target gene is from a pathogen such as a virus, wherein the target gene is associated with a disease in a mammal such as a cancer associated gene, wherein the target gene is selected from a transcribed, non-transcribed, coding, non-coding, exon-containing, regulatory or promoter sequence, wherein the double stranded region lacks a polyadenylation signal and wherein a composition comprises said RNA.

Werther et al. teach a multivalent antisense molecule targeted to two sequences of a target gene IGFBP or targeted to two or more sequences in different target genes such as IGFBP-2 and IGFBP-3 (see column 3). Werther et al. does not each a partially double stranded RNA comprising two or more different double stranded RNA sequence that are complementary to two or more sequence of at least one target gene. Werther et al. does not expression of said double stranded RNA from an expression vector.

Fire et al. teach double stranded RNA wherein the duplex regions of the RNA are capable of hybridizing with the target gene wherein the length of the duplex regions are from 25 to 400 bases (see columns 7-8). Fire et al. teach expression vectors comprising T7 polymerase promoters and teach the target gene may be derived from any cell of any organism wherein the organism may be a plant, animal or human (see column 8, lines 12-20). Fire et al. additionally teach the target gene may derived from any pathogen or any cell already infected by a pathogen such as HIV for example (see column 10, lines 8-18). Fire et al. teach the use of double stranded RNA for RNA inference is an effective alternative to antisense methodologies.

Heifetz et al. teach production of a double stranded interfering RNA comprising introducing into plant cells DNA sequences encoding a sense RNA strand and an antisense RNA strand into an expression vector wherein the sense and antisense RNA strands are complementary to each other and form a double stranded RNA (see page 8). Heifetz et al. teach the complementary regions can be 15, 50 or 500 nucleotides in length (see page 11). Heifetz et al. teach the DNA sequences are preferably operably linked to one or more promoters wherein the promoter is a heterologous promoter (see page 10 last paragraph to the top of page 11). Heifetz et al. teach the DNA sequences that form the double stranded RNA are inserted into the same vector wherein the sequences encodes a sense and an antisense strand or the DNA sequences that encode a sense strand or an antisense strand are in separate vectors (see pages 8-9). Heifetz et al. teach viral vectors can be used to introduce the DNA molecules into the plant cells (see page 11) and further teach methods of altering the expression of a target gene by introducing a vector comprising said DNA sequences as stated above (see pages 12-13 and Examples 1 and 3).

It would have been obvious to one of skill in the art to make a multitarget double stranded RNA wherein said double stranded RNA targets at least one or more than one target gene.

One would have been motivated to make a multitarget double stranded RNA targeted to two or more sequences of at least one target gene because certain target sequences are capable of mutation and targeting multiple sites on a target gene is advantages for effective therapeutics. Further, one would have been motivated

because certain diseases are triggered by expression from similar genes and therefore co-suppression, as taught by Werther et al. is an effective method. One would have been motivated to use double stranded RNA because Fire et al. teach double stranded RNA capable of initiating RNA interference is more sequence specific alternative to reducing expression of a target gene than antisense type mechanisms (see columns 1-3). One would have had a reasonable expectation of success given that Werther et al. teach construction of multitarget antisense and Fire et al. and Heifetz et al. teach gene inhibition using double stranded RNA wherein said duplex region is complementary to said target gene and wherein said double stranded RNA is expressed using expression vector comprising one or more promoters.

Werther et al., Fire et al. and Heifetz et al. do not teach an expression vector comprising a RNA pol III promoter.

Thompson teaches expression of therapeutic RNAs such as ribozymes, antisense RNA using RNA pol III based expression cassettes (see column 4, lines 11-20). Thompson teaches that in order for therapeutic RNAs to be effective, sufficient amounts must accumulate in the appropriate intracellular compartments (see column 10, lines 18-25). Thompson further teach pol III based expression cassettes are more attractive for expressing RNAs because pol III produces functional RNAs found in both the nucleus and the cytoplasm, are likely to be expressed in all tissue types and accumulate to much greater levels in cells (see column 10, lines 27-39). Thompson teach these advantages of pol III expression cassettes are desired for expressing RNAs *in vivo* and more particularly antiviral RNAs *in vivo* (see column 10, lines 41-50).

Thompson further teach production and accumulation of RNA transcripts produced from a pol III expression cassette in human 293 cells (see column 15 line 55 to column 16 line 9).

One of skill in the art would have been motivated to incorporate a RNA pol III promoter into the expression vector since Thompson teach pol III promoters are more attractive for expression of RNAs in all tissue types and the accumulation in the cells is greater from a pol III based expression vector. Moreover, both Heifetz et al. and Fire et al. teach expression vectors used for producing double stranded interfering RNA can comprise different promoters and Heifetz et al. specifically teach that promoters vary in their ability to promote transcription and one of skill in the art would choose a suitable promoter depending on the host cell system utilized (see page 15). Therefore, one would be motivated to use a pol III promoter for expression in mammalian cells, as taught by Thompson.

Thus, in absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Response to Applicants arguments

Re: Claim Rejections - 35 USC § 102

The rejection of record of claims 107-108, 113-119, 121, 123, 125, 127-138, 141-148, 156-159, 163, 165, 167, 168 and 170-172 under 35 U.S.C. 102(b) as being

anticipated by Taira et al. (U.S. Patent No. 5,500,357) is withdrawn in view of the new grounds of rejection above.

The rejection of record of claims 107, 109, 111-117, 119, 121, 123-137, 139, 141-143, 144-148, 156-157, 159, 163, 165, 167, 168 and 170-173 under 35 U.S.C. 102(b) as being anticipated by Chen et al. (Nucleic Acids Research 1992) is withdrawn in view of the new grounds of rejection above.

The rejection of record of claims 150-155 under 35 U.S.C. 102(e) as being anticipated by Taira et al. (US 2005/0197315) is withdrawn in view of the new grounds of rejection above.

The rejection of record of claims 107,117, 119-120, 137, 157, 159-160, 164 and 166 under 35 U.S.C. 102(e) as being anticipated by Ruiz et al. (U.S. Patent No. 5,912,149) is withdrawn in view of the new grounds of rejection above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached at 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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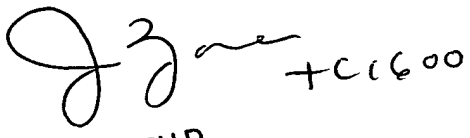

JANE ZARA, PH.D.
PRIMARY EXAMINER

Kimberly Chong
Examiner
Art Unit 1635